



Breath-holding test in subjects with near-fatal asthma. A new index for dyspnea perception[☆]

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Summary

Rationale: Identification of asthmatic subjects with low perception of dyspnea (POD) that are at higher risk of hospitalization, near-fatal and fatal asthma could improve their management.

Objective: Create a simple procedure that facilitate the recognition of low POD.

Methods: We enrolled near fatal asthma (NFA) subjects and a wide spectrum of non-NFA subjects. Each subject was asked to stop breathing at end-expiration. Dyspnea was assessed by a modified Borg scale. To design the new index, we combined the Borg score at the end of the voluntary breath-holding maneuver with the airway limitation. The equation was as follows: $FEV_1/FVC\% / (\text{breath-holding time in seconds} / \text{final Borg score} - \text{basal Borg score})$.

Results: Eleven NFA subjects (4 females) aged 21–73 yr and 55 non-NFA (14 severe, 18 moderate and 23 mild asthmatic subjects) completed the study. The threshold value of the index that could predict POD is <12 . The mean (\pm SD) of the new index perception was significantly lower in NFA group ($n = 11$; 5.21 ± 3.59 ; vs. $n = 55$; 13.67 ± 11.08 ; $P = 0.006$). This threshold value had 100% sensitivity and it best discriminated between mild and NFA groups. The negative likelihood ratio (when the index ≥ 12) was zero. A result ≥ 12 represented an almost null probability of poor POD.

Conclusion: The breath-holding test is simple and rapid. Its negative likelihood ratio was zero. Accordingly, a test result of 12 or greater might exclude the probability of poor perception of dyspnea in subjects with stable asthma.

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Introduction

An alteration in the ability of asthmatic patients to perceive symptoms in their day-to-day life will influence negatively in the management of asthma due to an underestimation of the symptoms severity.¹⁻³ The awareness that early events portend an increasingly severe condition is important for timely treatment. This fact determines that, the delay in instituting treatment is the single most important factor contributing to death from asthma.⁴ In this regard, a reduced chemosensitivity to hypoxia and blunted perception of dyspnea during resistive loading in subjects that had had a near fatal asthma attack (NFA) was confirmed by Kikuchi et al.² This is also, supported by a study in children with a history of life threatening asthma that had a significantly decreased slope in their resistive load magnitude estimation curve.⁵ More recently, Magadle and colleagues prospectively confirmed that asthmatic subjects with low perception of dyspnea (POD) are at higher risk of hospitalization, near-fatal and fatal asthma.⁶ All of these findings pointed to perception as being a key factor in the overall management of asthma.

Breath-holding time has been applied to evaluate the control of breathing and the sensation of experimentally induced dyspnea.^{7,8} It was hypothesized that those patients who have experienced an NFA attack should report a lower perception of dyspnea under other conditions, specifically those related to breath-holding maneuver, compared to non-NFA asthma patients. The breath-holding maneuver has been also used to detect the influence of emotion on breathlessness in participants with asthma.⁹

Accordingly, the main aim of the present study was to create a perception index by assessing the perception of dyspnea during the breath-holding test in subjects with asthma.

Methods

Subjects

Outpatient asthmatic subjects attending the center were considered to participate. Subjects with prior NFA, whom during the previous 12 months had exacerbations were included. Near fatal event was defined as follows: orotracheal intubation due to respiratory arrest during an asthma attack or acute respiratory acidosis with hypercapnia >45 mmHg. None of the subjects had glottic dysfunction syndrome, aspirin-induced asthma or had received

β -blockers, central depressants, or sedatives prior to NFA. The control group included non-NFA subjects that was classified according to WHO/NHLBI report.¹⁰ None of the subjects had a history of other respiratory disease than asthma, nor did they use any other pulmonary medications than inhaled corticosteroids, short- and long-acting β_2 agonists. All subjects were nonsmokers or ex-smokers (for more than 12 months, with less than 5 pack-yr). They specifically refrained for receiving sedatives, CNS depressants, thyroid hormones, and progestational treatment. The subjects were studied during a clinically stable period.

None of the subjects had experienced an exacerbation or a respiratory infection or need to increase their treatment for at least 4 weeks. All the treatments were withheld for 12 h and short- and long-acting bronchodilators for 6 and 24 h, respectively before each visit.

Measurements

Self administered asthma quality of life questionnaire (AQLQ) was completed.¹¹ After a 10 min rest, arterial oxyhemoglobin saturation was measured with a pulse oximetry (BCI International, Waukesha, WI). Then, each subject was asked "How does your asthma feel right now?" and Which is the level of your dyspnea? using a modified Borg scale (from 0 to 10) to take a basal rate of respiratory sensation.¹² Immediately after, the breath-holding test was explained. The subject was asked to stop breathing at end-expiration and to hold his or her breath with a nose clip for as long as possible without encouragement, while looking to the modified Borg scale. The end-expiration that should correspond to FRC was determined by observing the pattern of tidal breathing during at least 30 s. The breath-holding maneuver was repeated a maximum of 3 occasions separated by at least 2 min if there was $>10\%$ difference in time between the first and second test. The total breath-holding time was measured with a chronograph. The intensity of any discomfort was marked with the modified Borg scale (10 = maximal discomfort) just at the breaking point that also defined the end of breath-holding maneuver. The test with the longer voluntary breath holding was selected for analysis. The greater fall in oxygen saturation during the test was registered.

The equation that was applied to calculate the new index is as follows:

$FEV_1/FVC\% / (\text{breath-holding time in seconds} / \text{final Borg score minus basal Borg score})$. The rationale for the above equation was sustained in that the

FEV₁/FVC% ratio was a measure of chronic airway limitation related to low dyspnea perception.¹² Then, we put breath-holding time in the denominator because we assumed that the longer the holding time, the lower the dyspnea perception.⁸ Finally, we divided breath-holding time by the difference in Borg score because a minor Borg score difference may indicate poor symptoms perception, resulting in a lower index. In other words, the lower the index was, the lower the symptoms in near fatal asthma is <12. This threshold value was selected because it had 100% sensitivity and best discriminated between mild and NFA groups and it was confirmed by the receiver operating characteristics (ROC) curves analysis.

Spirometry was performed with DatoSpir-200 (SibelMed®; Barcelona, Spain) and predicted values were obtained from Morris et al.¹³

Histamine challenge test was only performed in the group of subjects who had suffered a NFA event using the method of tidal breathing.¹⁴ The intensity of any discomfort was marked with the modified Borg scale immediately before each FEV₁ measurement. The perception score at the 20% fall in FEV₁ (PS₂₀) was determined by interpolation of the two last perception scores. The slope and intercept of the regression of Borg score and the percent fall FEV₁ were calculated for each subject.

The study was approved by the institutional research committee, and each subject gave informed consent to participate in the study.

Statistical analysis

The total breath-holding time was defined as the time from the command of breath holding to the breaking point.⁸ Unless otherwise stated, data are expressed as mean (SD). Differences between groups were assessed with one way analysis of variance and all pairs with Tukey Kramer multiple comparisons test if $P < 0.05$ and if the Bartlett's test for homogeneity of variances was not significant. When variances were not homogeneous, Kruskal–Wallis nonparametric ANOVA test and Dunn's multiple comparisons test was done.

Nonparametric unpaired Student's *t*-test was used to compare normally distributed variables, and the Mann–Whitney *U* test was used for other variables. Differences were assessed with two sided tests, with an α level of 0.05. Spearman rank correlation was used to test the relationship between variables. A value of $P < 0.05$ was accepted as indicating a statistically significant difference.

A true positive result was defined as occurring when a patient's index predicted low perception (<12) and the subject actually belong to NFA group. A true negative result as occurring when the index predicted belonging to mild asthma group (≥ 12) and the subject actually belong to this group. A false positive result as occurring when the index is <12 in mild asthma and a false negative result when the index is ≥ 12 and the subject is included in the NFA group. The reproducibility of the test according to Bland and Altman¹⁵ was randomly assessed in 9 NFA and 9 non-NFA subjects by measuring twice at least 15 days apart. The positive and negative likelihood ratios of the test results were calculated to assess the performance in diagnosing the target disorder.

Results

Three NFA patients were not enrolled in the study; one due to pregnancy, other could not stop β agonists at least 6 h before the challenge test and the last one denied to participate. Two subjects of the non-NFA group refused to participate. Eleven near fatal asthma subjects (4 females) aged 21–73 year completed the study. Nine of them had required orotracheal intubation due to respiratory arrest during an asthma attack. The other two patients had acute respiratory acidosis with pH = 7.26; PaCO₂ = 56 mmHg; base excess = −3 and pH = 7.28; PaCO₂ = 58 mmHg and base excess = −2, respectively. The distribution according to WHO/NHLBI¹⁰ categories of the 55 non-NFA subjects was as follows: 23 patients (15 females) as mild persistent or intermittent, 18 subjects as moderate (8 females) and 14 (10 females) as severe asthma. Table 1 shows the general characteristics of the 4 groups. Mild asthmatic subjects were younger than severe and NFA groups ($P < 0.05$). The median time elapsed since the near fatal event was 12.0 (95% CI = 7.8–48.5) months. The history of asthma in years was significantly longer in NFA and severe groups than in mild asthma group ($P < 0.05$). The mean FVC and FEV₁ in liters were not significantly different between Mild and NFA groups. Both variables, FVC and FEV₁ of the severe group were lower than the means of the other 3 groups. Means of FEV₁% predicted¹³ were significantly different between the groups with the exception of NFA vs. moderate group. The mean FEV₁% pred of non-NFA subjects ($n = 55$; mean = 75.4 ± 21.1) was similar to NFA subjects (74.9 ± 12.6 ; $P = 0.68$). The means of FEV₁/FVC% were different between severe vs. mild and

Table 1 Subject characteristics.

	Near fatal	Severe	Moderate	Mild
Male/female	7/4	4/10	10/8	8/15
Age (yr)	46.3 (16.8)	46.4 (17.5)	35.22 (13.3)	30.4 (12.9)
Yrs of asthma	31.4 (16.1)	30.1 (13.4)	18.3 (13.2)	17 (14)
FEV ₁ (L)	2.34 (0.86)	1.34 (0.69)	2.38 (0.46)	2.97 (0.86)
FEV ₁ % pred	75 (13)	48.1 (13.7)	75.6 (15.1)	91.9 (7.5)
FVC (L)	3.4 (1.14)	2.18 (1.05)	3.46 (0.66)	3.92 (1.1)
ICS dose	945.5 (465.5)	571.4 (601.8)	347.4(338.9)	—
AQLQ	5.5 (1.2)	5.11 (1.27)	5.12 (1.34)	5.97 (1.26)
<i>New perception</i>				
Index	5.21 (3.59)	6.43 (4.22)	11.45 (7.97)	19.68 (12.91)
Pulse rate	72.5 (4.7)	78.5 (16.0)	74.9 (6.0)	75.6 (8.4)
Percent fall O ₂ sat	4.1 (4.1)	4.0 (1.6)	4.4 (4.5)	2.6 (1.9)

Means (SD). See the text for statistical differences between groups.

moderate (ANOVA; $P < 0.0001$, Bartlett's = 0.98). There was no difference in AQLQ between groups despite the grading of severity. The % fall in O₂ saturation at the end of the test was similar as well as the basal pulse rate (Table 1). Nine NFA, 6 severe, and 3 moderate asthmatic subjects repeated the test within 2 and 12 weeks apart for testing reproducibility. The calculated coefficient of repeatability was: 10.98; that is twice the standard deviation of the differences of the 2 measures (5.49). The mean difference was 0.46 and according to Bland and Altman¹⁵ it was not significantly different from zero. All the differences were less than 10.98; then the index could be considered as reproducible. Figure 1 shows the plot of pairs of measurements according to Bland and Altman.¹⁵

Comparisons of basal and final Borg scores between groups were not significantly different. The unpaired t test showed that the mean breath-holding time of the NFA group was significantly longer than the mean of the non-NFA group (34.46 ± 13.02 ; $n = 11$ versus 24.11 ± 9.76 ; $n = 55$; $P = 0.0035$); but the likelihood ratios (1.6 and 0.2) indicated a poor diagnostic accuracy for altered POD. The mean time of breath-holding was only different between NFA and moderate groups (ANOVA $P = 0.036$ and Tukey Kramer $P < 0.05$; Table 2). None of the means of the perception index components were statistically different between mild and NFA groups. The mean of the new index perception was significantly higher in mild asthma group in comparison with near fatal asthma and severe groups (Kruskal Wallis ANOVA test = $P < 0.001$). When comparing NFA versus non-NFA subjects, the new index perception was significantly lower in NFA group (5.21 ± 3.59 ; vs.

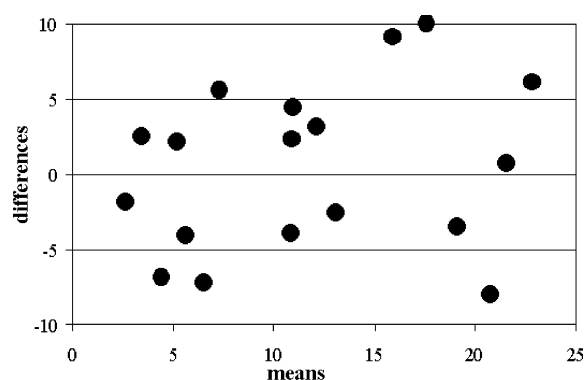


Figure 1 Reproducibility of the test. Differences between two separated measurements of the new index; and the means of both measurements were plotted. All the differences were less than twice the SD of the mean difference (10.98); $n = 18$; mean difference = 0.46 ± 5.49 . Y-axis (differences) denotes differences between repeat measurements of the new index. X-axis (differences) denotes means of replicate measurements of the new index.

13.67 ± 11.08 , $n = 55$; $P = 0.006$). The threshold value selected for predictive index of low breathlessness perception was 12 (if a subject had an index value < 12 , he was considered as hypoperceiver). The sensitivity of this index was 1.00; specificity was 0.44 and the negative predictive value was 1.00 for discriminating between non-NFA ($n = 55$) and near fatal asthma group. The area under the ROC curve for the new index, which summarizes the performance of that index in detecting poor POD was 0.76 (standard error = 0.089) for the set derived from the data on 55 non-NFA and 11 NFA subjects. The positive likelihood ratio was 1.77 and the negative like-

Table 2 Components of the new index.

	Near fatal	Severe	Moderate	Mild
Basal Borg score	1.41 (1.41)	2.0 (2.08)	1.28 (1.76)	0.57 (1.41)
Final Borg score	3.91 (1.97)	4.29 (2.56)	4.67 (2.52)	6.0 (2.52)
FEV ₁ /FVC% ^a	68.6 (9.0)	60.9 (8.2)	69.2 (8.0)	75.9 (8.7)
BH in seconds ^b	34.5 (13.0)	24.9 (8.6)	23.2 (10.5)	24.3 (10.2)
New perception Index	5.21 (3.59)	6.43 (4.22)	11.45 (7.97)	19.68 (12.91)

Means (SD).

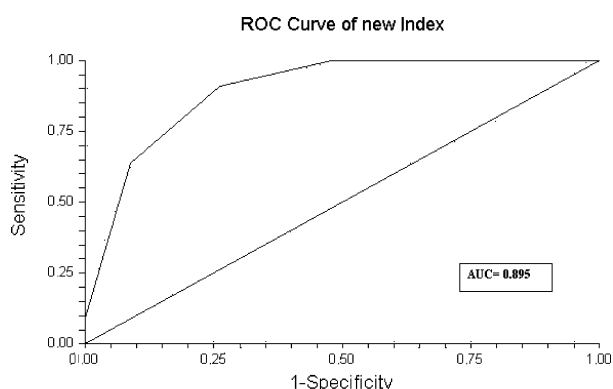
^aFEV₁/FVC% severe vs. moderate = $P < 0.05$. Severe vs. mild = $P < 0.001$.^bBH = breath-holding test. BH time NFA vs. moderate $P < 0.05$.

Figure 2 Receiver operating characteristic (ROC) curve analysis for the index, generated by plotting the proportion of true positive results (sensitivity) against the proportion of false positive results (1-specificity) for each value of the new index including the 23 mild asthmatic subjects and 11 near fatal asthma subjects. The area under the curve is expressed in the box as the proportion of the total area of the graph.

likelihood ratio (index ≥ 12) was zero. In other words, a test result lower than 12 was 1.77 times as likely to have poor POD. Importantly, a result ≥ 12 generated an almost null probability of poor POD. When the set of data for calculating the area under the ROC curve was mild asthma group and NFA group, the AUC was 0.895 ± 0.067 (Fig. 2). There was a significant correlation between the new index and FEV₁% pred ($n = 66$, $r = 0.41$; $P < 0.001$) but it did not correlate with age, history of asthma, AQLQ, budesonide dose, FVC and time elapsed since the NFA event.

The mean log P_{c20} FEV₁ histamine was -0.097 ± 0.61 mg/ml (geometric mean $P_{c20} = 0.80$ mg/ml; range = 0.05–4.74). The geometric mean PS_{20} in Borg units was 2.53 (range = 0–5.98) while the mean Borg score at the end of the histamine test

was 3.27 ± 1.9 . The mean slope and mean intercept of the regression of Borg score/percent fall FEV₁ were 0.062 ± 0.065 and 1.28 ± 1.18 , respectively. The difference between final Borg score and post-saline solution Borg score was 1.26 ± 1.44 . There was neither correlation between PS_{20} FEV₁ in Borg units and the new index ($r = -0.36$; $P = 0.3$; $n = 11$) nor between slope and intercept with new index ($r = -0.27$ and 0.07 ; P : NS).

Discussion

The present study introduced a new index to rule out low perception of dyspnea in asthma. Until now, no reliable predictive equation or simple screening tool had been developed to identify asthmatic patients with low POD. This index had a sensitivity and a negative predictive value of 100% for near fatal asthma group when a threshold < 12 was applied. The negative likelihood ratio was zero and this ratio excluded the presence of low POD when the index result was ≥ 12 .

This new index has some interesting features. Firstly, it was intrasubject reproducible, simple and rapid. It could be easily calculated and readily available. It just required a spirometer, a chronometer and a modified Borg dyspnea scale from zero to 10 units. This index might be used to rule out poor perception of dyspnea. Poorly perceived asthma is one of the main factors associated with death from asthma.¹⁶

The ROC curve provided a powerful means of assessing a test's ability to discriminate between two groups of patients, with the advantage that the analysis did not depend on the threshold value selected. The area under the ROC curve was quite large (0.895) between mild and NFA groups and this analysis circumvented the main problem inherent

in the technique of classic decision analysis, namely, dependence on the threshold value that was selected. The negative likelihood ratio equal to zero denoted that the probability of poor POD was extremely low when the index was ≥ 12 . Hypothetically, this index should be prospectively assessed as a marker of high risk by correlating with the lack of activation of cortical neurons as it has been studied using respiratory-related evoked potential techniques.¹⁷ Diminished activation of cortical neurons might be reflected by a low index result. Unfortunately, breath-holding time alone showed unsatisfactory likelihood ratios in order to change the probability for diagnosing altered POD.

Diminished perception of dyspnea and airway narrowing had a relevant role in treatment delay, near fatal events, and death during acute severe asthma. In this regard, Magadle and colleagues⁶ found in 2 years of follow up that 29 asthmatic patients with poor perception of dyspnea (POD) suffered 13 near-fatal attacks and six deaths. These authors strongly recommended to measure POD at least once in all asthmatic subjects with either technique, the method of breathing against added resistance or added threshold loads, or the methacholine/histamine bronchoprovocation test. Bijl-Hofland and colleagues showed that the histamine-induced bronchoconstriction test identified more patients as poorest perceivers compared to the threshold loading test.¹⁸ Within the bronchoprovocation test, many alternative indexes to $PS_{20}FEV_1$ have been described for detecting subjects with poor POD or prone to near fatal asthma such as the percentage fall in FVC/log $Pc_{20}FEV_1$,¹⁹ the change in Borg scale as the mathematical difference between PS_{20} histamine and baseline dyspnea²⁰; and the slope and intercept from linear regression of Borg/% fall in FEV_1 .²¹ The simplest marker for NFA was the $FEV_1 < 79\%$ predicted or the FEV_1/FVC ratio of $< 75\%$ that was recently published by Gelb et al.²² We did not find any difference in $FEV_1\%$ predicted between NFA group ($n = 11$; $74.9 \pm 12.6\%$) and the rest of the population studied ($n = 55$; $75.4\% \pm 21.2$; $P = 0.68$). In contrast the new index perception in NFA group was significantly lower (5.21 ± 3.59) than in the rest of the subjects ($n = 55$; 13.67 ± 11.08 ; $P = 0.006$). Other procedures attempting to recognize poor POD and NFA subjects has been published such as a Borg score < 6 at peak cycle exercise,²³ and the failure of inspiratory occlusion to elicit the P_1 peak of the respiratory-related evoked potentials that was found in a subpopulation of children with prior NFA.¹⁷ Davenport et al suggested that an altered neural processing of inspiratory load information could explain the failure in recognizing the airway

obstruction.¹⁷ Webster and Colrain²⁴ investigated the long latency evoked potentials and found a markedly reduced respiratory and auditory P3 components in subjects with asthma compared with the control group without asthma. They sustained that a general sensory deficit is involved in the mechanism of perceptual processing in asthmatic subjects.

Despite the fact that it is still not known whether the altered POD is acquired or inherited, NFA subjects should not be considered as having an irreversible and inevitably lethal phenotype.²⁵ Furthermore, there was some evidence that inhaled corticosteroids and combined therapy might improve symptoms perception.^{26,27}

The new index was not statistically different between severe, moderate and NFA subjects. Undoubtedly, the best example of blunted perception was near fatal asthma¹⁻³; but also a poor POD might be found in other categories of asthmatic patients. Importantly, poor perception of breathlessness was associated with: severity of asthma in outpatients with different grading of asthma,²⁸ particularly those with recurrent exacerbations²⁹; with elderly asthmatic patients,³⁰ with long-standing airflow limitation,¹² and during ICS dose reduction.³¹ This strong relationship between severe and long-standing airway obstruction with low POD lend support the inclusion of the FEV_1/FVC ratio in this new index. Simultaneously, severity became the major confounding factor of a low POD index, such that we found similar index means in NFA and severe group (Table 1), and by the other way, mild asthma group showed the higher mean of the new index perception.

Our study has some potential limitations. It was not a case control trial, although there were no significant differences in the equation components between NFA and mild asthma groups. The perceived sensation of voluntary breath-holding is somewhat different from symptoms during an spontaneous asthma exacerbation. Killian and colleagues suggested that in acute asthma, the stimulation of free nerve endings in the airways may cause an additional drive to breathe leading to air hunger and breathlessness in the same way as a rising $PaCO_2$ due to holding one's breath. These symptoms were not discriminated, suggesting a common mechanism as expected.³² We did not find a correlation between PS_{20} and FEV_1 in Borg units and the new index probably due to the fact that these procedures could not comprise the different aspects of the complex process of symptom perception. The investigators that performed the tests were aware of the patient condition and this issue could have caused some bias. However, the

interpretation of the results was judged at the end of the study. Finally, as severity and long-standing airflow limitation^{12,28,29} were intrinsically related with loss of POD the new index might not be able to discriminate poor perception from severe airway obstruction.

Reduced awareness of methacholine/histamine-induced bronchoconstriction was only described in one of 3 studies of near fatal asthmatic patients. Ruffin et al.,³³ showed a mean value (SD) for the NFA group ($n = 43$), 0.86 ± 0.56 mm/percent change in FEV₁, that was significant less than for the non-NFA asthmatic group, 1.13 ± 0.72 mm/percent change in FEV₁, $P = 0.012$. Boulet et al.³⁴ found a mean PS₂₀ FEV₁ of 3.0 ± 0.7 in 13 NFA subjects and 2.5 ± 0.4 in the control group. Turner and colleagues³⁵ found no difference between NFA and admitted patients without NFA event. Salome et al.³⁶ studied the perception of airway narrowing in a large population sample involving 697 adults who underwent challenge testing with histamine. They found that subjects with asymptomatic AHR did not differ significantly from subjects with current asthma either in the mean fall in FEV₁ (24% vs. 27%) or in the median Borg score at the end of the challenge (4 vs. 4). Our data from NFA subjects were: mean fall in FEV₁ = 28% and the median Borg score was also 4. Then, measurement of POD during histamine challenge test was similar between our NFA group and asymptomatic AHR subjects studied by Salome et al.³⁶ It was evident that there was no definite cut off point to determine altered POD from the histamine challenge test. Furthermore, since the geometric mean PC₂₀ of the different series of NFA was 0.23 mg/ml,³⁷ subjects received few histamine doses and thus there were a few points to construct the lineal regression Borg score/% fall FEV₁ in order to calculate the slope and intercept. These variables seemed to be more sensitive in detecting changes in perception.^{18,21} Bijl-Hofland et al.¹⁸ found that 25% of the patients with the poorest perception value (assessed by bronchial provocation) had a slope of <0.4 . Accordingly, the mean slope of the regression Borg/% fall FEV₁ was 0.062 in our NFA group, confirming poor POD. But, this does not mean that patients with a slope of <0.4 are actually absolute poor perceivers.¹⁸ In this regard, Salome et al.²⁶ found a very low Borg/FEV₁ slope (0.09) in 35 non-NFA subjects that was indicating poor POD, while their PS₂₀ FEV₁ was high (5.66), suggesting good perception. All of these contradictory results reinforced the fact that, there was no gold standard or unified reference test result to consider a subject as a poor perceiver or not.

In conclusion, the breath-holding test index was simple, and readily available. According to the

negative likelihood ratio, the test result of 12 or greater might exclude the probability of poor perception of dyspnea in subjects with stable asthma.

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